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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,636	11/25/1997	ELAZAR RABBBANI	ENZ-53(DIV-3	4642

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/978,636	RABBBANI ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-255,258 and 262* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-255,258 and 262* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 23 March 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 31 May 2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Applicants Arguments re: 35 USC § 112

Claims 245-254 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and is repeated for the same reasons of record as set forth in the action mailed 31 May 2005.

Claim 245, and those dependent thereon are drawn to nucleic acid constructs which comprise a nucleic acid sequence that encodes a non-eukaryotic polymerase that further comprises a non-native-intron.

To be clear, the instant rejection is based on the supposition that there is inadequate support for the term "non-eukaryotic polymerase". In response to this rejection, applicants have asserted generally that support can be found on page 81 and page 87. However, this is not

convincing, since the support in the indicated location provides only a few examples which are non-eukaryotic, but are not considered to teach the genus of non-eukaryotic. While it is agreed that applicants have provided examples of non-eukaryotic polymerases, such examples are not considered to support the concept that eukaryotic polymerases were ever intended to be excluded, or in contrast, that archaeobacteria polymerases were to be included. A few examples from very broad genus of non-eukaryotic polymerases are not considered to provide support for the entire genus of non-eukaryotic polymerases, and the rejection is maintained therefore.

All other arguments are moot in view of the new rejections below.

New Rejections-- - 35 USC § 112

Claims 245-255, 258, and 262 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant invention is drawn to a nucleic acid construct which comprises a nucleic acid sequence which encodes a non-eukaryotic polymerase, said sequence further comprising an intron, non-native to said polymerase, wherein said intron sequence is within the sequence encoding said polymerase and wherein said polymerase is (a) incapable of expression in an incompatible cell, whereas said incompatibility is due to failure of expression of said polymerase due to the presence of said non-native intron and (b) is capable of producing more than one copy of a nucleic acid sequence from said construct when introduced into a compatible cell.

The phrase "wherein said polymerase is (a) incapable of expression" is considered to be vague and indefinite, because while nucleic acids encoding polymerases may be capable of expression, polymerases themselves are not capable of expression.

Claims 245-255, 258 and 262 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to a nucleic acid construct which comprises a nucleic acid sequence which encodes a non-eukaryotic polymerase, said sequence further comprising an intron, non-native to said polymerase, wherein said intron sequence is within the sequence encoding said polymerase and wherein said polymerase is (a) incapable of expression in an incompatible cell, whereas said incompatibility is due to failure of expression of said polymerase due to the presence of said non-native intron and (b) is capable of producing more than one copy of a nucleic acid sequence from said construct when introduced into a compatible cell. The invention is also drawn to such constructs which encode not a polymerase, but rather any gene product that would be toxic to a cell that contain an inserted intron that counteracts its toxicity in incompatible cells, and wherein said intron is inserted immediately 3' to a (C/A)AG motif.

The specification does not provide support for the use of any intron, in any polymerase or any bacteriophage polymerase, or any conditionally toxic gene, in any incompatible cell because

the specification provides only minimal prophetic description and no examplification, of any particular intron, polymerase (including bacteriophage polymerase), or toxic gene, or cells compatible or incompatible for whom known structures exist that could be utilized having the claimed function. In determining whether adequate support is provided for the broad genera described above applicant is referred to the following passage from the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

As stated above, the specification provides only minimal prophetic description and no examplification, of any particular intron, polymerase (including bacteriophage polymerase), or toxic gene, or cells compatible or incompatible for whom known structures exist that could be utilized having the claimed function. The specification provides for the use of T3, T7 or SP6 polymerases, and also for the use of certain "consensus" splice donor and acceptor sites for inserting introns. Applicants prophetically suggest that intron "insertion at any of these sites in a gene coding region should not affect subsequent removal of the processing element in a compatible cell." (page 84 of the instant specification).

However, there is significant unpredictability in such intron removal, since such a process requires a complex interaction between the nucleic acid construct and the already existent

cellular machinery. A review article by Balvay et al. indicates that the splicing machinery is highly dependent upon recognizing and interacting with such secondary structures in making the splice. Balvay et al. indicates that the addition of a secondary structure to an existing mRNA can cause the cell to splice at a point not normally spliced at, while removal of such a structure can cause splicing to be eliminated (for example see pages 165 bridging to 166). Furthermore, Balvay indicates that the exon plays a significant role in splice site recognition by the cellular splicing machinery. Since one of skill would understand that the nucleotides in the exon remain in the mRNA (or ribozyme) after splicing, applicants claimed nucleic acid constructs, *following splicing*, would likely therefore contain elements of these exon recognition sites. Such unpredictability indicates that the genus of nucleic acid constructs comprising any intron in any polymerase (or any bacteriophage polymerase), or any toxic gene, and that are active or inactive depending on whether they are found in cells that are compatible or incompatible is very large. The fact that the specification discloses only prophetic examples and a few species of polymerases and donor/acceptor splice sites is not considered to constitute a sufficient representative sample of the genus of such constructs. The claims are rejected therefore.

Claims 245-255, 258 and 262 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is as described above.

Applicants' specifically claim that the inserted and inactivating intronic sequences will be spliced out, a process the specification indicates will be carried out by the cellular machinery that normally operates to splice introns out of pre-mRNA sequences. Applicants indicate that such splicing restores native activity to previously inactive proteins. However, the specification as filed does not provide any nucleic acid constructs for which this has actually been shown. Applicants specification does not provide sufficient guidance or examples that would enable a skilled artisan to make the disclosed nucleic acid constructs containing sequences that are spliced out by cellular machinery. Although the specification prophetically considers and discloses making and using such constructs, such a disclosure would not be considered enabling since introducing intervening sequences into nucleic acids alters their secondary structure, which makes their ability to be cleaved by the splicing machinery unpredictable. The specification has not resolved such issues, since no exemplified constructs that contain intervening sequences and are inactive therefore, and by which later processing inside the cell restores activity. Applicants have simply not shown that such intervening sequences can be spliced out to restore any activity to previously inactive polymerases (or any toxic protein for that matter). For the reasons cited below, the ability of the cell to splice out such engineered sequences to restore polymerase or toxic activity is considered to be an unpredictable exercise. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following reference is cited herein to illustrate the state of the art of catalytic nucleic acids. In particular, it is demonstrated that the complex secondary structures of nucleic acids are responsible for their intron excision activity, and furthermore, that predicting the ability of the cellular splicing machinery to splice out precise intervening sequences from disrupted sequences with variable secondary structures such that native activity is restored is considered unpredictable, because the splicing machinery is sensitive to the presence or absence of such structures.

The instant invention is wholly dependent upon the ability of the splicing machinery of the cell to interact with such secondary structures in splicing out the intervening sequence to activate the native polymerase or other activity. A review article by Balvay et al. indicates that the splicing machinery is highly dependent upon recognizing and interacting with such secondary structures in making the splice. Balvay et al. indicates that the addition of a secondary structure to an existing mRNA can cause the cell to splice at a point not normally spliced at, while removal of such a structure can cause splicing to be eliminated (for example see pages 165 bridging to 166). Furthermore, Balvay indicates that the exon plays a significant role in splice site recognition by the cellular splicing machinery. Since one of skill would understand that the nucleotides in the exon remain in the mRNA after splicing, applicants claimed constructs, which embrace a very broad genus of all polymerases or bacteriophage polymerases, or any toxic protein, *following splicing*, would therefore likely contain elements of these exon recognition sites. Since applicant has not shown that their intervening sequence is spliced out cleanly, or that such disrupted constructs can ever be activated in the cell, and because the prior art indicates

uncertainty with respect to the proper splicing of applicants disrupted nucleic acids, one of skill could not depend upon the teachings of the specification or the prior art for overcoming these problems.

Therefore, as indicated above, because secondary structures of RNA vary unpredictably with sequence, and because such secondary structures have a pronounced effect on RNA splicing, and finally because the replacement of even a few nucleotides on a mRNA can abolish all activity of the translated protein, it is maintained that neither the specification nor the prior art arms one of skill with the information necessary to engineer sequences into nucleic acid constructs that will be reliably spliced out to result in a protein with native activity restored.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would therefore require the *de novo* determination of intervening sequences that can be fully spliced out without leaving behind any nucleotides that might interfere with native activity. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS

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PRIMARY EXAMINER